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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,585	07/26/2001	Klaas Poelstra	POELSTRA	2750

545 7590 10/22/2002

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	9

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/868,585	Applicant(s) POELSTRA ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *24-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-23 and 36 filed on July 8, 2002 is acknowledged. Claims 24-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The traversal is on the grounds that claim 24 incorporates the special technical feature of claim 1 and that claims of Groups III-V are linked together by the special technical feature of claim 1, therefore all of the claims 1-36 should be examined on the merits. Claim 24 of Group IV lacks novelty and does not make a contribution over the prior art, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

Restriction is required under 35 U.S.C. 121 and 372.

The MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each (see MPEP 802.01). In the instant situation, the inventions of Groups I-VI are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

The literature search, particularly relevant in this art, is not co-extensive, because for example, Group II is drawn to a product. Groups I, III, IV, V and VI are drawn to different methods that require different reagents, parameters and endpoints. Clearly different searches and issues are involved in the examination of each Group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

2. Claim 1 is objected to because "AP" should be changed to "alkaline phosphatase". The proper name of a term should be used at the first occurrence in the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-23 and 36 recite the phase "degree of AP occupancy of LPS". It is unclear as to what the applicant is referring? Clarification as to the meaning of this term is required.

4. Claims 1-23 and 36 recite the phase "degree of form of a patient". It is unclear as to what the applicant is referring? It appears that Applicant is referring to "from a patient". Clarification is required.

5. Regarding claim 21, the phrase " i.e." which means "such as" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

6. Regarding claim 13, the phrase "e.g." which means "for example" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-23 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al *(U.S. Patent No. 5,928, 624, published July 27, 1999)* in view of Poelstra et al *(American Journal of Pathology, Vo. 151, No. 4, October 1997).*

Claims 1-23 and 36 are drawn to a method of diagnosis of the onset of endotoxemia or sepsis due to the gram-negative bacterial infection said method comprising monitoring of the degree of alkaline phosphatase (AP) of lipopolysaccharide (LPS) binding sites on AP in a sample of tissue or fluid derived from a patient wherein

the degree of AP occupancy is associated with presence or absence of gram-negative bacterial infection.

Wright et al teach a method of diagnosis, prognosis or monitoring of a gram-negative infection, endotoxin-mediated sepsis or septic shock. Wright et al teach the method comprises measuring the level of lipoprotein particles that contain lipid exchange protein that is characterized by being capable of facilitating an exchange of lipopolysaccharide into the high density lipoprotein particles and comparing the level to a level in a patient at an earlier time wherein an increase in the level indicated greater probability of a positive outcome of the sepsis. Wright et al also teach that the measurement used in the method of the invention is a functional measurement of the capacity of plasma from a subject to neutralize LPS and the measurement can be performed by immunoassay technique or it's equivalent using a specific binding partner (column 6, lines 1-15). Wright et al teach the detection or measuring of the invention can comprise determining the capacity of biological fluid (e.g. plasma or serum from a subject to neutralize LPS activity) (column 18, lines 46-48). Wright et al teach that alternatively, detection according to the invention can be assayed by immunoassay. Wright teach that antibodies reactive with a component of the lipoprotein or the LPS exchange protein or both can be prepared and optionally labeled with enzymes, a compound the fluoresces and/or a radioactive element, and may then be introduced into a biological sample from a mammal believed to be suffering from endotoxin-mediated sepsis (column 18, lines 62-67 and column 19, lines 1-2).

Wright et al do not teach monitoring of the degree of alkaline phosphatase (AP) of lipopolysaccharide (LPS) binding sites on AP in a sample of tissue or fluid derived from a patient wherein the degree of AP occupancy is associated with presence or absence of gram-negative bacterial infection.

Poelstra et al teach that alkaline phosphatase (AP) is a membrane-bound enzyme that can dephosphorylate various phosphorylated substrates (page 1163). Poelstra et al teach that exogenous AP is able to attenuate the inflammatory response upon lipopolysaccharide (LPS) in rates and mice (page 1163). Poelstra et al teach that endotoxin is a natural substrate for AP (page 1163). Poelstra et al teach that LPS dephosphorylation by AP was assayed by measurement of inorganic phosphate release (page 1164). Poelstra et al teach that LPS from both *E. coli* and *Salmonella minnesota* was dephosphorylated at physiological PH level by phosphatase activity in intestinal cryostat section and the measured enzyme activity was shown to be due to AP because the localization of the reaction product corresponded exactly with AP activity as demonstrated using conventional methods (page 1167). Poelstra et al teach that AP is able to dephosphorylate lipid A and this important because removal of one phosphate group from lipid A moiety attenuates the biological effects of the whole LPS molecule (page 1167). Poelstra et al teach that LPS plays a crucial role in sepsis caused by gram-negative bacteria (page 1167). Limitations such as "wherein the sample is taken from an individual during hospitalization", "wherein the sample is take a number of times over a period of time and the data are compared thus revealing the level of AP occupancy over time", "wherein the period of time is as long as the individual is at risk of

infection i.e. during hospitalization or post trauma recovery" are being viewed as limitations of design choice.

It would be *prima facie* obvious at the time the invention was made to add the alkaline phosphatase as taught by Poelstra et al to the method of diagnosis, prognosis or monitoring of a gram-negative infection, endotoxin-mediated sepsis or septic shock of Wright et al because Poelstra et al teach that LPS from both *E. coli* and *Salmonella minnesota* was dephosphorylated at physiological PH level by phosphatase activity in intestinal cryostat section and the measured enzyme activity was shown to be due to AP because the localization of the reaction product corresponded exactly with AP activity as demonstrated using conventional methods and that the removal of one phosphate group from lipid A moiety attenuates the biological effects of the whole LPS molecule (page 1167). Therefore, it would be expected barring evidence to the contrary, that the measurement of AP activity on LPS can be used to diagnosis the onset of sepsis due to a gram-negative bacteria infection because Wright et al teach that the measurement used in the method of the diagnosis, prognosis or monitoring of a gram-negative infection, endotoxin-mediated sepsis or septic shock is a functional measurement of the capacity of plasma from a subject to neutralize LPS and the measurement can be performed by immunoassay technique or it's equivalent using a specific binding partner (column 6, lines 1-15).

Pertinent Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure (*Poelstra et al, Hepatology, Vol. 24, Nov. 4, Pt.2, 1996 and Poelstra et al, Laboratory Investigation, Vol. 76, No. 3, 1997).*

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
October 2, 2002

MARK NAVARRO
PRIMARY EXAMINER